Is the Creation and Development of Biotech SMEs Localised? Conclusions Drawn from the French Case

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ABSTRACT. The article examines the localisation effects within biotechnology, concentrating in particular on the French case. The paper has two strands of analysis. The first presents a detailed statistical survey of the French biotechnology sector. Among other things, the survey shows that a) localisation effects within France are strong, b) in terms of dependence on local cluster infrastructures (especially universities and related public research institutes), most firms progress from an entry stage in which they are very dependent on local cluster infrastructures, to a mature phase in which their networks become more national/international in focus and c) French firms can be grouped into four general types of firms, ranging from "type 1" growth oriented product firms, to "type 2" niche market players, " type 3" subsidiaries of larger firms, and "type 4" firms that have been acquired. Localisation effects differ across these firms, esp. across type 1 (international) and type 2 (very localised) firms. The second strand of analysis consists of a review of the localisation and related cluster literature, with implications drawn out for localisation and knowledge spillovers within biotech clusters. It examines the relative effects of scientific centres proximity and compares them to the public policy of start-up creation.

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Introduction

The structure of biotechnology production and research, a field straddling several industrial sectors (pharmaceuticals, chemicals, agriculture, production of research services, etc.) is still largely unexplored. French and European statistical apparatus is ill-equipped to describe its evolution and our knowledge is based essentially on studies by private consultancy firms (Ernst & Young, in particular). Yet biotechnology is one of the fields that public authorities wish to develop, at both European and national levels (e.g. the 5th Framework Programme and the Bioregio Programme in Germany, respectively).

By enhancing our knowledge of the characteristics of this sector we are in a better position to measure its impact on economic growth and to design appropriate tools for research and industrial development policies. In this context the spatial dimension seems essential, for it is often claimed that the creation and diffusion of technologies are a strong local component with regard to both the spatial concentration of technological activities and the close links that are generally highlighted between science and industry (see, e.g., Feldman, 1994).

In the U.S. the biotechnology sector has developed around centres of scientific excellence (Zucker and Darby, 1997; Zucker et al., 1997a, b), for the mobility of researchers from academic research centres towards the private sector is a vehicle for the diffusion of knowledge and a powerful incentive for start-ups. Economic and tax incentives for high-tech entrepreneurs have produced impressive results in Quebec, now North America's third major region for the establishment of biotech firms. The French case is more complex to analyse, for the state defines an economic and

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fiscal policy for the entire country, while the regions have other economic policy tools to promote biotechnology development in certain areas of production. As Genet (1997) shows, the development of biotechnopoles has been moderately successful. Although the Strasbourg and Clermont Ferrand technopoles have developed fast, stimulating the emergence of numerous SMEs (Small and Medium-sized Enterprises), it seems that this has not been the case elsewhere.

The aim of this paper is to gain insight into the development logic of biotechnology SMEs in France. Several dimensions warrant analysis if we are to grasp the driving forces behind the development of biotechnology in a given geographic area (local, regional, state). Is scientific excellence enough to promote the creation of high-tech SMEs? Do economic and fiscal policies offer adequate incentives for the creation of biotech SMEs? If so, what explains local agglomerations? If, on the contrary, local policies are the determining factor, what tools can local economic policy use? Do SMEs benefit from local externalities, related to the public or tacit dimensions of skills and knowledge? Without claiming to provide answers to all these questions, we have used the French case to investigate whether the creation and development of biotechnology enterprises[1] is localised.

The first part of this text is an overview of biotech firms in France and their development, based on a survey carried out in 1999. It also presents a first attempt to explain the spatial disparities observed. The second part explores the development trajectories of these SMEs and the impact of geographic and organisational proximity in a context in which knowledge is often tacit.

1. French biotech SMEs: Spatially polarised growth

1.1. *Biotechnology: a small industrial sector*

On 1 January 1999 France had just over 400 biotechnology SMEs employing 15,000 people, with an estimated turnover of 2 billion Euros.[2] Estimates based on the survey initiated by the MENRT (Ministère de l'Éducation Nationale, de la Recherche et de la Technologie, the French ministry in charge of research) are consistent with information published by Ernst & Young, although they indicate a higher number of firms in France. Average size in terms of number of employees is nevertheless similar (about 40 persons). All in all, biotechnology remains a small emergent sector compared to others such as agro-food (over 4,200 French firms with 372,300 employees and a turnover of 100 billion Euros) or pharmaceuticals (94,500 employees in 271 firms and a turnover of 30 billion Euros[3]) (S. Lemarié and V. Mangematin, 2000).

Small enterprises created recently

Results show that almost 70% of firms in the sample were created after 1990. This figure needs to be analysed with caution. The survey, conducted in 1999, takes into account only those firms still in existence at the time. Since the overall mortality rate of *high-tech* SMEs is close to 20% in the three years following their creation, we can estimate that the number of firms created in the 1970s which survived up to 1999 is lower than the number of firms actually created in those years. Yet, even if we consider that there is a bias in the transversal analysis, we note a sharp increase in the number of start-ups in the past decade. Firms that have existed for 20 years or more account for 12% of the sample, whereas more recent firms account for 69% of the total. Less than 20% of the firms were created between 1980 and 1990.

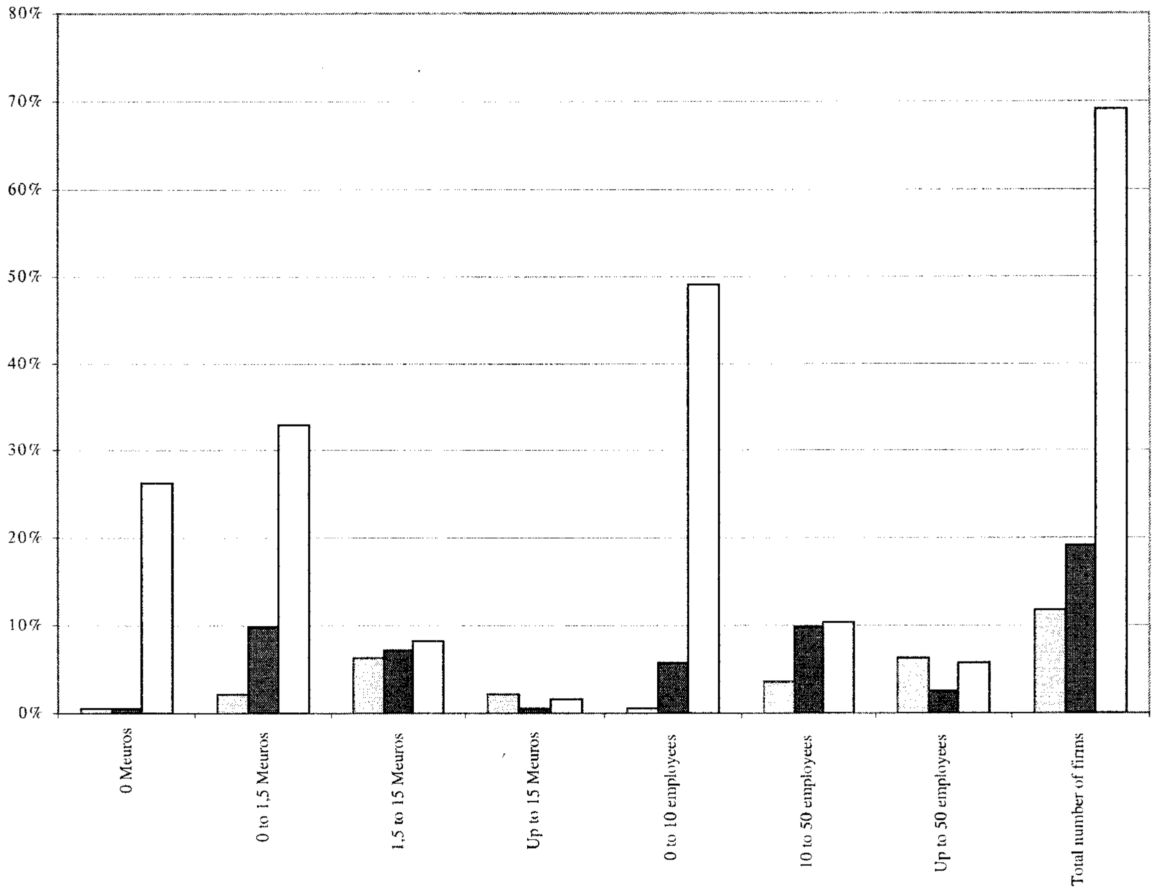
In general, the legal status (limited liability company-SARL (Société Anonyme à Responsibilité Limitée) Vs. Limited company-SA) is related to the firm's mode of development.[5] Although SAs (Sociétés anonymes) are the most prevalent legal form, 30% of start-ups in the sample chose a status that guaranteed them absolute control over capital while limiting capital investments.

The average number of employees in biotech-

TABLE I
Age and legal status of SMEs

	Age			
	Before 1980	1980–1990	After 1990	Total
Total	12%	19%	69%	100%

Source: MENRT Survey.



Source: Author's calculation.

Figure 1. Turnover and number of employees, in relation to age of the firm.

nology SMEs is 36, with a turnover of around 5 Million Euros. Thus, firms remain small in terms of both employees and turnover. 72% of firms have a turnover under 1.5 MEuros, as opposed to only 4% with over 15 MEuros. 24% have a turnover between 1.5 and 15 MEuros.

55% of firms have under ten employees, 14% only have over 50, and 31% have between 10 and 50. Although there is a slight discrepancy, at the time of setting up, between recruitment and the turnover it generates, employee numbers and sales of products and services remain very closely related. The majority of old established firms (founded before 1980) employ over ten people and have a turnover of more than 1.5 MEuros. Of the six firms with the highest turnover, three are old (Stago laboratories, Goemar laboratories and Solabia) and three are recent (Genset, Genevrier laboratories and Germicopa SA). Although age and size are related, it nevertheless seems that certain firms created during the past ten years have grown very fast, while this does not hold true for those established between 1980 and 1990.

The growth of the firm also depends on the targeted sectors that the firm is focusing. Table II presents the size of firms related to the targeted sector. It shows that most of the recent firms are targeting the pharmaceutical sector. The second sector in terms of number of firms and in terms of employees is the agriculture and agro-food sector. Firms which are involved in agricultural-biotech are older than those of the target pharmaceutical sector.

TABLE II
The size of firms by targeted sector

	Before 1980		1989–1990		After 1990		Total	
Targeted sector of activity	% of firms	Average number employees	% of firms	Average number employees	% of firms	Average number employees	% of firms	Average number employees
Agriculture/environment and pharmacy	5%	99	5%	28	16%	30	26%	42
Agriculture/environment, cosmetics	0%	0	0%	0	2%	8	2%	8
Agriculture/environment	0%	0	1%	12	5%	30	6%	25
Pharmacy and cosmetics	0.5%	110	1%	36	2.5%	4	4%	39
Pharmacy	3%	150	7%	64	26%	29	36%	53
Cosmetics	0.5%	98	2%	13	3%	9	5.5%	20
All sectors	2%	20	4%	22	14.5%	11	20.5%	14
Total	11%	108	20%	37	69%	23	100%	37

Source: Author's calculation.

Growth related to shareholding
Close to 40% of the firms are owned only by natural persons, most often by the founders and their family. Irrespective of their age, these firms develop more slowly than those with more diversified shareholders.

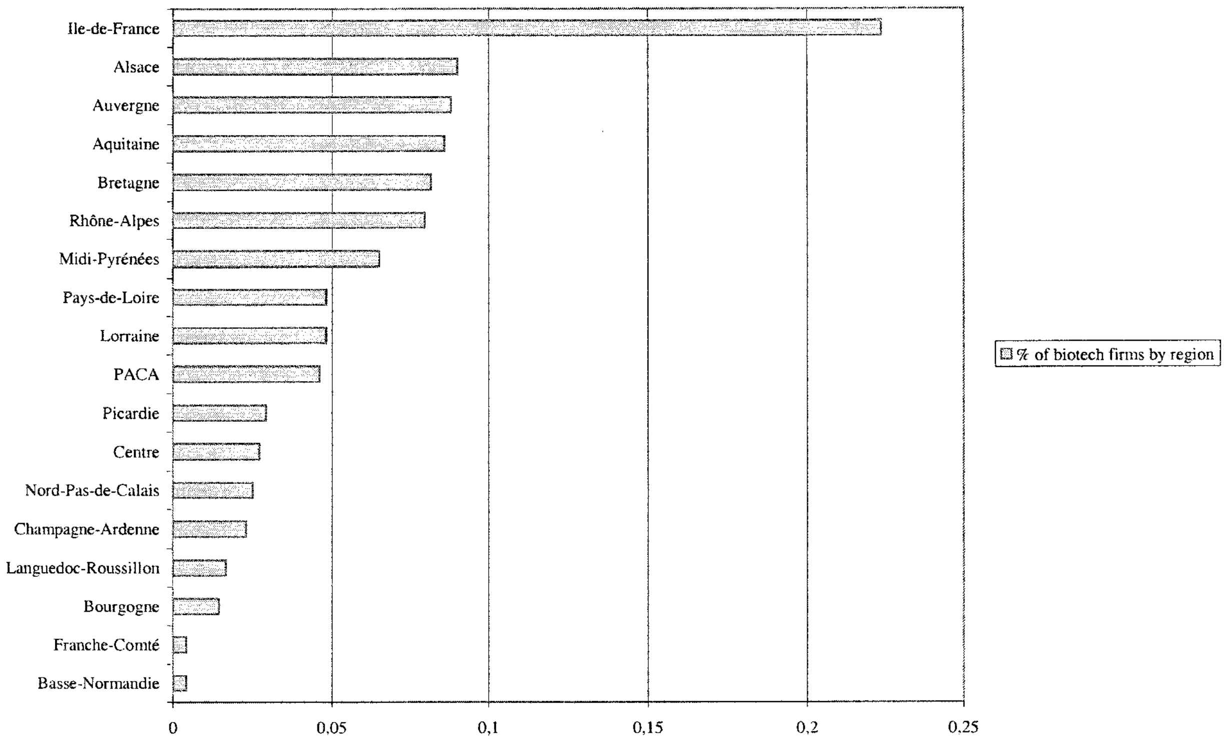
Those firms which depend on a parent company (over 50% of the capital held by another firm) grow much faster in terms of turnover, including the most recent firms. Differences are not substantial, however, in terms of employee numbers. We can therefore presume that the parent company constitutes a market in which the subsidiary is rapidly able to extract value from research under way.

The average size of those biotechnology SMEs which have a venture capital company among their shareholders is not different from that of other categories. Differences are substantial, however, when we analyse the age of firms. On the one hand, we see that venture capital firms withdrew their capital from the oldest companies when conditions were right. Thus, the average size of firms created before 1980 and in which venture capital companies remain shareholders, is smaller than the average in terms of both turnover and number of employees. On the other hand, for firms set up between 1980 and 1990, the average size in terms of employees is far greater when venture capital firms are shareholders. There are no significant differences for the most recent firms. For firms that have another firm as a shareholder, the average number of employees and average turnover are far greater than those of firms not in

TABLE III
Shareholders of biotechnology SMEs

		Average turnover		Average number of employees	
The following are shareholders	In % of the total	Yes	No	Yes	No
Venture capital firms	28%	41,982	28,683	35	35
Another company	41%	45,565	22,334	54	22
Including the parent company	24%	54,129	25,095	46	32
The public (company listed on the stock exchange)	3%	55,728	30,831	139	31
Only natural persons	38%	16,769	45,625	15	54

Source: Author's calculation.



Source: Author's calculation.

Figure 2. Percentage of biotech firms in each area.

this category. The same applies to the six firms listed on the new stock exchange.

1.2. *How can spatial disparities be explained?*

In France, development of the biotechnology sector remains concentrated on a few leading regions, as shown in Figure 2. While Ile de France remains dominant, especially as regards firms created around universities and Genomic Valleys, Alsace, Auvergne, Aquitaine, Brittany, Rhône-Alpes and Midi-Pyrénées are also regions in which biotech firms set up. Firms specialising in genome and drug development technologies are situated primarily in Ile de France, while firms in Aquitaine, Brittany and Auvergne focus more on agricultural-food related markets. The regions with the highest proportion of new firms are Auvergne, Rhône-Alpes and Ile de France, while firms in Alsace, Brittany and Centre are generally older. A degree of regional specialisation, albeit very small, emerges, especially around pharmaceutical and genome related technologies[5] in Ile de France and around agri-food related markets in Auvergne, Aquitaine and Brittany.

What are the reasons for localisation of biotech firms? Is the establishment of high-tech firms based on the presence close by of university and research centres with a reputation for excellence? Is it related to the establishment in the same geographical area of firms that use biotechnology, especially pharmaceutical firms? Or should the presence of biotech firms be imputed to the presence of technological platforms or facilities close by? It is worth exploring the reasons for these spatial disparities and seeking explanations in the economic literature devoted to phenomena of spatial polarisation or concentration. Two main categories of analysis are usually applied, based on research conducted in the framework of New Economic Geography and research on local technological externalities, respectively.

a) The first explanation is the one proposed by New Economic Geography (Fujita and Thisse, 1997), introducing the possibility of conjoint localisation of firms in the same space (a town, for example, but rather a region or area of production in the case under consideration here), at the expense of neighbouring or rival spaces. The suggested causes of this polarisation are multiple but we can identify two particularly important ones leading to the establishment of localised increasing returns (Krugman, 1991) which maintain a divergent process of localisation of activities. They are the existence of *indivisibilities and of the preference for variety*:

- *Indivisibilities* in production generate fixed costs, which can lead to the appearance of local economies related to an intensive use of materials (e.g. factories run on an eight-hour shift basis), to their location in certain places only (technological platforms, mines or fishing harbours, for example) or to the concentration of retail outlets;
- *Preference for variety*, which corresponds to the structure of monopolistic competition models, has two converging facets: on the one hand it generates an increase in the utility of consumers who derive more satisfaction from the fact that they have more choice and, on the other, it is a benefit to businesses which use more specialised semi-processed goods. In particular, consumers' demand for goods with a high level of differentiation enables firms producing ranges of similar products to position themselves in the same place and to aim for concentrations of potential customers and semi-processed goods available at a local level.

Analyses of increasing returns use two categories of secondary models, each of which emphasises a different property of factors of agglomeration. *The first group* focuses above all on the *importance of transport costs* to explain firms' localisation. Krugman (1991) shows that the existence of high transport costs leads to regional convergence, while low transport costs result in a concentration of localisation in one of the regions. Economies of scale are another important factor causing consumers to demand local goods. Both factors contribute to the establishment of circular causalities and, in particular, to the appearance of strong relations and causal links between firms and regions. *The second group* concentrates on the *importance of upstream-downstream trade relations* in the context of the production of goods. These vertical linkages are forces of agglomeration. Firms situated downstream provide a market for those situated higher up, which can encourage them to locate close by. Two types of linkage can be distinguished: "demand linkages" which result in an increase in the scale of production by downstream firms and benefit upstream firms whose demand increases accordingly; and "cost linkages" which cause an increase in the volume of production of upstream firms and can lead to a price decrease for firms situated downstream. These two elements together constitute an agglomerating force that depends only on the market. Venables shows that if vertical linkages are strong (or weak) and trading costs high (or low), there will be a tendency towards a single locality (or multilocalisation). Although the question of indivisibility is hardly relevant for small firms, the instrumentation involved in biotechnology can play a decisive part in the localisation of activities. A start-up cannot invest in heavy equipment that it will use only occasionally.

b) The second main explanation derives from the literature devoted to local technological externalities, sometimes also called geographic spillovers. The aim here is to try to ascertain the extent to which research and innovation have characteristics of spatial concentration, and to look for the causes of that concentration, especially in the localised nature of knowledge transmission. The idea is often held that two main types of approach can be distinguished here (Feldman, 1999): the first emphasises the coincidence between phenomena of localised growth and presence of technological externalities, while the second measures the geographic dimension of spillovers.

We can go further in the latter direction and examine the way in which empirical studies analyse mechanisms of spatial concentration of innovation activities (Autant-Bernard and Massard, 1998). It then appears that the analysis of geographic spillovers often proves to be difficult at an econometric level, and that it is risky inferring questions of localisation from indicators such as patents, the number of innovations or even relations between geographic areas and R&D expenditures (Anselin et al., 1997). We can nevertheless identify a number of conclusions of such research:

- Innovation in a given region is closely related to public and private research spending in the region (Feldman, 1994), including in sectors that are not research-intensive (Mangematin, 1999);
- Innovation in a given region is not only related to public and private R&D spending but also to the region's entire technology transfer infrastructure (presence of technological centres, of technology transfer agencies, etc.) (Feldman, 1994; Llerena and Schaeffer, 1995). Thus, the presence of complementary activities generates more spillovers and reduces costs and risks related to firms' innovation;
- There are no eviction effects between public and private R&D spending. They enhance each other to create areas of expertise (Jaffe et al., 1993).

Traditional explanations in terms of spillovers remain unsatisfactory. Economic theory remains indecisive as to the ability of SMEs to capture externalities. Whereas conceptual studies emphasise the concept of absorptive capacity, empirical work describes a correlation between intensity of presence of university research in a given geographic area and the propensity to innovate, irrespective of the sector concerned. It sheds little light on the verified presence of local externality effects. Audretsch, Feldman and Stephan (Audretsch and Feldman, 1996; Audretsch and Stephan, 1996) made a specific analysis of high-tech sectors and showed that, in sectors where innovation is based on science, geographic links are weaker. 70% of relations between biotech firms and universities are not based on geographic proximity. Studies on relations between biotech firms and universities are not, however, transposable to choice of location when firms set up. In this phase, relations between start-ups and firms in their "natural" network are fundamental and location is often in the entrepreneur's "natural" environment. Acs et al. (1997), on an infra-regional scale, highlight the effects of local spillovers owing to the presence of a large university and reputable research departments.

It seems, therefore, that the analysis is very different at the time of the start-up, when the survival and development of the firm depend on the founder's close network of relations, and later when the firm is established and builds sound relations in the same scientific, productive and commercial network.

2. Different mechanisms of proximity, depending on the type of firm

2.1. *Definition of different forms of proximity*

The term "proximity" is used more and more often in economic analyses and tends partially to replace "distance" and "localisation". Does it have an effective theoretical content? The question is important in our research because it concerns the evaluation of the extent to which proximity plays a part in the localisation of start-up SMEs and in their performance. This type of approach enables us to assess the degree of spatial concentration in the creation and development of these firms and hence to define complementary national and regional economic policy tools. While the term proximity is sometimes used in the models considered above – Economic Geography and geography of innovations – it can have different meanings, depending on the research and the authors. That is why it is necessary first clearly to define the concept of proximity in the two senses used here: geographic proximity and organisational proximity, as well as the concepts related to this approach (Torre and Gilly, 2000).

Geographic proximity

Geographic proximity concerns spatial separation and relations in terms of distance. Relating essentially to the localisation of firms it includes the social dimension of economic mechanisms or what is sometimes called functional distance. In other words, it consists of more than the reference to natural and physical constraints, clearly inscribed in its definition, since it also encompasses aspects of social construction, such as transport infrastructure, which impact on access time, or financial resources allowing for the use of certain communication technologies. Incubators and facilities for assisting and supporting business creation play an essential role in the geography of localisation as presented in spatial economic models. Most often, the term covers proximity based on the presence of local infrastructure or markets. In this case innovations appear in clusters.

Organisational proximity

Organisational proximity is based on two types of logic that can be qualified as similitude and affiliation, respectively. With the logic of affiliation, actors belonging to the same area of relations (firm, network, etc.), in which different kinds of interaction take place (e.g. cooperation or circulation of knowledge), are close in organisational terms. With the logic of similitude, actors who resemble one another, i.e. who possess the same area of reference and share the same knowledge, so that the institutional dimension is important, are close in organisational terms. In the first case, membership of the same set is conditioned by the effective nature of coordination; in the second, proximity is related to the "resemblance" of representations and modes of functioning. Far from being antinomic, these two aspects can sometimes be reconciled, particularly when affiliation initially based on horizontal relations of an intra-industrial nature are subsequently concretised in an increase in interdependence between organisations, signifying greater similarity (or institutional proximity) between the players.

In the case of biotechnology and many high-tech activities, it is the logic of affiliation that plays an important part, particularly in the circulation of knowledge between organisations – a circulation based on a mode of functioning similar to that of inter-individual relations.

Localised cluster and circulation of tacit knowledge

It is at the articulation between geographic proximity and organisational proximity that fruitful interaction occurs, in terms of both spatial and technological developments, i.e. developments which promote both the growth of high-tech firms and their spatial concentration within certain areas of scientific production or research. Some studies thus seem to show that new firms set up in areas where cooperative relationships can be formed, close to the places where the people concerned were trained, and that their success depends on the maintenance and development of the researcher-entrepreneur's relations with the academic community.

The idea is often put forward that this search for geographic and organisational proximity is based on the tacit dimension of knowledge, which implies close relations between actors in the research and innovation process. Since Polanyi's famous statement: "We know more than we can tell", the tacit dimension of knowledge has been the object of numerous theoretical developments. There is no lack of empirical examples, e.g.: learning to use new software alone by following the manual or learning from an expert does not produce the same results. The former method is slower and more laborious whereas the latter requires less effort and offers a more global view far sooner. Hatchuel and Weil (1995) define different types of know-how (doing know-how, understanding know-how and combining know-how) and show that they are acquired in different ways. Know-how is transmitted essentially through interpersonal interaction, as is understanding know-how. Combining know-how is more the fruit of experience and the acquisition of a very broad culture.

Saviotti (1994) has a similar argument when he characterises knowledge according to its degree of contextuality. The more knowledge is context-related, the narrower its scope will be. As a result, it does not allow the identification and understanding of expertise outside the initial context. More fundamental knowledge is broader in scope and allows for the assimilation of diversified skills. This idea is consistent with explanations by Rosenberg (1990) on firms' investments in basic research. Abstract knowledge is one of the conditions for being able to develop extensive competitive intelligence. Thus, the more fundamental the knowledge developed in-house, the more easily the firm will absorb a wide variety of knowledge. Conversely, if the firm has a low absorptive capacity, it will be able to assimilate less varied knowledge. Mangematin and Nesta (1999) show that the circulation of people is an essential dimension in collaboration between organisations. It is particularly important when the partners have different capacities for absorbing scientific knowledge.

It is relevant to explore the way in which geographic proximity is somewhat hastily equated with tacit knowledge, the former supposedly favouring the diffusion of the latter (Rallet and

Torre, 1998). The circulation of tacit knowledge is based on the circulation of people and, in that context, the temporary staff of public laboratories (PhDs and *post-docs*) plays a key part. Circulation of PhDs and post-doctoral students between organisations and between research laboratories enables the organisations in which they work to acquire knowledge produced in other laboratories. In such cases, knowledge and know-how are acquired not through the replication of experiments carried out elsewhere but through the recruitment of researchers on a temporary or permanent basis. Thus, collaboration between public laboratories and firms leads to the exchange of PhDs and technicians. When staff from a firm are sent to an academic laboratory, they are trained in a specific technique required by the firm and mastered by the laboratory. The same applies to university laboratories which dominate certain complementary techniques; in-depth knowledge of key techniques is circulated and diffused through the exchange of staff. The recruitment by firms or laboratories of qualified staff with specific skills lacking in those organisations corresponds, for the university or laboratory that trained those individuals, to a diffusion of knowledge via the circulation of people among institutions. Our own empirical research on the engineering sciences and life sciences shows, however, that the impact of organisational proximity may vary, depending on the case (Mangematin, 2000). The engineering sciences have a long tradition of cooperation between public laboratories and firms.

The role of regional public policy in initiating biotech start-ups

The circulation of tacit knowledge is one of the explanations of the existence of clusters. Zucker et al. (Zucker et al., 1997b) address the mechanisms by which knowledge spillovers are realised. They show that ideas are embodied in individuals who have the skill, knowledge and know-how to engage in technological advance. Their papers focus on the human capital of key individual rather than on the average human capital in the local labour market. The start-ups in biotech are localised in regions in which this intellectual capital resides. These star scientists embody knowledge breakthrough techniques that are initially only available at the lab of the scientists, making them costly for others to obtain the use.

Almedia and Kogut (1997) extend this approach of intellectual capital by considering the inter-firm and inter-mobility of star patent holders in order to trace the transfer of ideas in semi-conductor industry. Their results suggest that the localised intellectual capital is key in the development of the new industry and that knowledge generates externalities that tend to be geographically bounded within the region where the scientists reside.

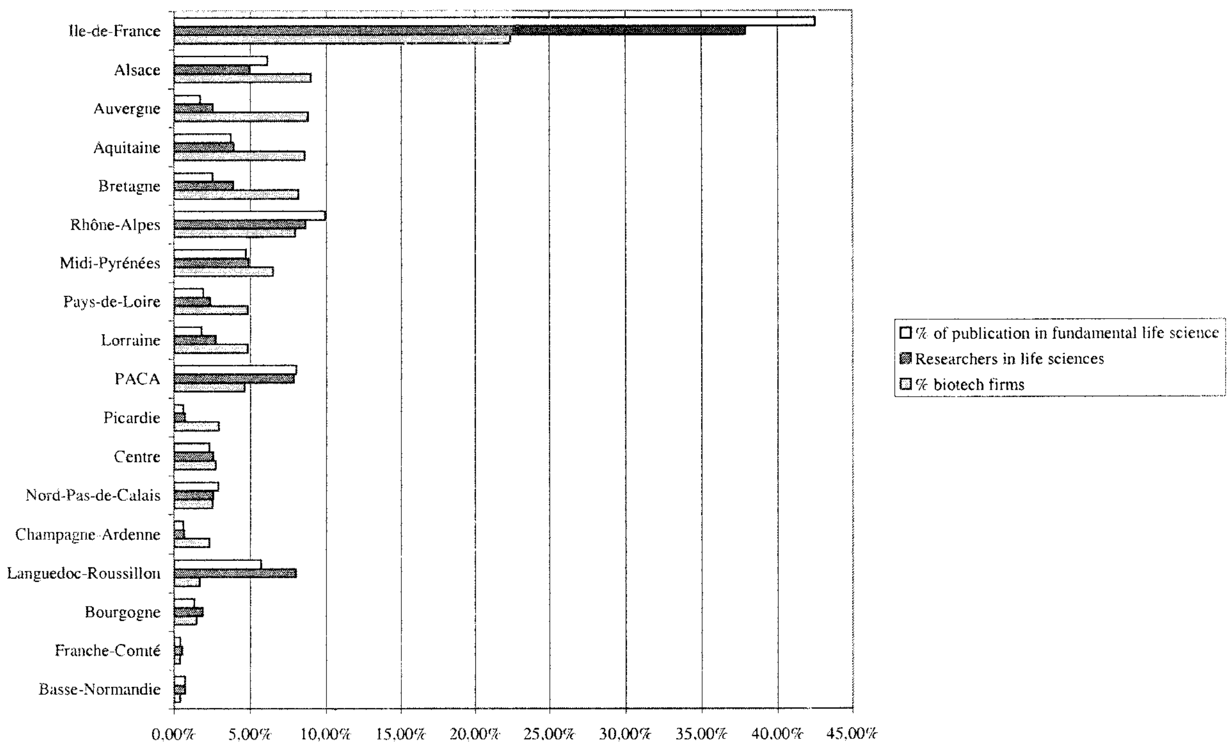
In the French Biotech sector, the situation seems quite different. Figure 2 shows that the creation of biotech firms is localised in the main economic regions, i.e. Ile de France, Rhone-Alpes and Midi-Pyrénées. However, Figure 3 demonstrates that the localisation of biotech start-ups is neither proportional to the number of researchers in academia in the region nor proportional to the global number of publication in the same area.

Scientific clusters do not explain completely the localisation of biotech firms in France. Amongst other factors, two elements are key elements to understand the localisation of firms: the heterogeneity of biotech firms (Mangematin, 2000) and the public policy to encourage start-ups creation.

2.2. *Localisation of Biotech firms: a combination regional public policy and different trajectories of firms*

Public policy in favour of firms creation

Monsan (2000) proposes an up-dated analysis of the recent history government of policy to support biotech. At the beginning of the 80s, the objective of the French public support for biotech was dedicated to encourage a number of industrial sectors such as agro-food and seeds. In this way, public funding was used to revitalise groups working in the life sciences and bring them together, at the same time assisting them to rapidly integrate molecular biology and genetic engineering methodologies. To strengthen relations between public research and industry, biotechnology transfer centres were set up, for example in the public sector research (PSR) – Institut Pasteur, CNRS (Conseil National de la Recherche scientifique), INRA etc. Subsequently, several of



Source: Author's calculation.

Figure 3. Comparison between the number of biotech firms and the academic research potential by regions.

them became research and technological innovation centres (CRITTs: Centre Régional d'Innovation et de Transfer de Technologie).

Lastly, national public policy in favour of biotech was also designed to support start-ups. A number of companies were created using venture capital. These include Transgene, founded in Strasbourg in 1979, Immunotech (Marseille, 1982) and BioEurope (Toulouse, 1984).

After this initial phase, the major concern of public policy as it was redesigned in 1985 was to preserve the transversal nature of biotechnology while concentrating funds on four priority domains: the food industry, health, IT and international relations. With a budget of 16.5 MEuros over 3 years, the "Expansion" biotechnology programme largely funded small biotech companies created during the Eighties, enabling them to boost their own research activity (most often within a close partnership with French state research establishments), and to accelerate the development of innovative products. But despite all these efforts, the biotechnology revolution announced at the beginning of the 80s was slow, and the results of research already engaged in terms of turnover and job creation, remained erratic.

At the beginning of the 90s, the authorities decided to directly support the big industrial groups' research and development programmes, in order to accelerate the commercialisation of research through concrete action. This was the objective of the BioAvenir programme launched in 1991. In bringing together Rhône Poulenc and various public research establishments, BioAvenir constituted an innovative partnership between the private and public sectors.

In the mid 90s, national and regional public authorities launched new biotechnology programmes. Their aims were to reinforce the partnership between private and public research, and also to encourage the creation of new growth companies by facilitating research scientists' mobility between the sectors and by creating facilities (technological platforms and incubators). This was a strong incentive to business creation, and at the time was backed up by renewed interest in biotechnology from the finance community, in particular for gene therapy, neuro-degenerative disease treatment and genomics. 1996 saw the arrival of the EASDAQ (European Association of Securities Dealers Automated Quotation), a European financial market for high growth high-tech companies, together with that of the Paris Bourse's "Nouveau Marché", both factors contributed to the development of numerous biotech company creation projects.

Different tools of public policy have been mobilised at the national and at the regional level. The effects of the local public policy can been seen in very dynamic regions such as Auvergne, Alsace, Aquitaine where the science base appears to be weaker than in other regions (like Rhone Alpes for example). As it has been shown by Genet (1997), these regions are those which have invested in a technolopole to support start-up creations. It could also be the specialisation of the local area, genomics for example in Strasbourg which leads the economic development of the region.

Different trajectories, on which geographic and organisational proximity have a different impact

The majority of firms active in the biotechnology field in France are relatively young – mostly founded after 1990 and some less than two years old – and small (under 10 employees), with a maximum turnover of 1.5 million Euros (see Tables IV and V). Their future is therefore still largely unpredictable although it will probably correspond to one of the four types of trajectory identified in our sample.

Our study (Lemarié and Mangematin, 2000) reveals one successful trajectory (Type 1), representing a minority of cases, and three more disparate trajectories. Some firms have a regular but non-exponential growth of employee numbers and turnover, although they have existed for over ten years (Type 2); others are affiliated to a parent company (Type 3); and large industrial corporations (Type 4) have bought others out.

Type 1: Successful start-ups – a small minority of firms

28 firms in our sample (14.4% of the 194 respondents), considered to be the flagships of the French biotechnology industry, grew very fast. Active primarily in the fields of genome research and drug development, their main outlet was the pharmaceuticals market. Whether they were founded about ten years ago (11 of them) or before 1980 (12 of them – close to half), all of them have over 50 employees. Yet these firms employ less than a quarter of all employees in the biotechnology sector. Moreover, only eight of them (i.e. 4.1%) have a turnover of more than 100MF (15 million Euros) and only six of those are listed on the stock exchange (Biodome, Cerep, Chemunex, Genset, Quantum Appligene, Transgène).

Their development is based primarily on the presence of investors in national and international capital. Venture capital companies, present from the start, have been active in orientating these companies, setting them on a course of rapid growth. By extending the number of subscribers beyond the inner circle, firms are able to benefit from advice, contacts, human capital and an introduction into networks with which they are unfamiliar or which required too much effort to explore. Fewer than 30% of the 194 respondent firms have a venture capital company among their

TABLE IV
Biotechnology SMEs: unequal development

	Firm created	From 0 to 10 people	From 10 to 50 people	> 50 people	Total
Firms	Before 80	4	7	12	23
	80–90	13	19	5	37
	After 90	103	20	11	134
	Total	120	46	28	184

Source: Author's calculation.

TABLE V
Distribution of staff

Turnover (million Euros)	Under 1.5	1.5 to 15	Over 15
No. of firms and %	144 (74.2%)	42 (21.7%)	8 (4.1%)
Percentage of employment in the sector	24.8	53.3	21.9

Source: Author's calculation.

shareholders. Moreover, quoting of the firm on the stock exchange enables venture capital firms to sell their shares and withdraw their capital, an indispensable condition for the perpetuation of venture capital financing of biotechnology firms. The presence of venture capital firms in these companies favours the development from essentially domestic organisational proximity (family capital, network of entrepreneurs) to organisational proximity with networks comprising all actors on the biotech scene.

For maintaining technological skills, fast-growing firms rely on collaboration with French or foreign universities and with public institutions such as the CNRS (Conseil National de la Recherche Scientifique) or INRA, rather than basing their development on a product/specific market combination. Collaboration with other firms, especially pharmaceutical companies, enables them to extract value from their technologies. Geographic proximity is clearly of little importance for this type of firm which is situated in an international market for the diffusion of its products, and maintains relations with laboratories situated elsewhere. The need to be connected to major communication axes shows the full importance of relations of organisational proximity and the crucial nature of introduction into networks of strong relations. Note, however, that these firms' need to be close to centres of excellence to benefit from public research spillovers through interpersonal relations and international exchange maintained by academic laboratories. The quality of a firm's interaction with players in the same geographic area will depend on scientific life in that environment. To attract the best researchers, PhDs and post-doctoral researchers, all potential collaborators, firms are well advised to take advantage of neighbouring centres of academic excellence. This applies to their creation as well as their development.

Type 2: Stable businesses in niches

More than half (53.3%) of biotech employees work in firms that have followed a different development trajectory to that of Type 1 firms. Founded in the 1970s, generally as limited liability companies (SARL) or limited companies (SA) with private persons only as shareholders, their turnover today is between 10MF (1.5 million Euros) and 100MF (15 million Euros). These firms (e.g. Cayla and Anda Biologicals) employ between 10 and 50 people, derive a large share of their turnover from export and invest close to 25% of their turnover in research. Active mainly in the pharmaceuticals market, they have a relatively broad technological base maintained both by internal research and by relations with French and foreign universities. These firms, which have been in existence for several years, do not seem to have the intention of becoming leaders in their field on a worldwide scale; they nevertheless represent an alternative development path for biotech companies.

These companies are characterised by a strong reference to geographic proximity when they seek research or market resources in their immediate environment. In this case, relations with users of products and services are formed on the basis of geographic proximity. However, they do not neglect resources from organisational proximity, as attested by their membership of networks.

Type 3: Firms affiliated to a parent company

One of the strategies of pharmaceutical or seed companies is to create biotechnology firms, either alone or as a joint venture. Biotechnology is in fact a high-risk business whose development requires specific skills. Moreover, small structures are more flexible and easier to adapt to major changes triggered by the production of new scientific knowledge. Finally, investing in a biotechnology enterprise also enables firms to set up in a country with a view to taking advantage of its research "externalities" and of new markets.

Thus, major French or foreign companies (e.g. Limagrain or Rhône Poulenc, and Monsanto, respectively) have invested in subsidiaries specialised in biotechnology, either to secure a foothold in France (e.g. BioSepra, Bachem Biochimie and Diagnostica Stago) or to separate biotechnology from the firm's main business (e.g. Syral, Biosem and Limagrain Genetics). These firms, which benefit from the captive market represented by the parent company and from the network of markets to which the latter provides access, have a faster-increasing turnover than that of independent firms. It seems here that geographic proximity plays a relatively minor part in this type of strategy, based above all on the parent company's internal network. Organisational proximity is the most important factor, for geographic incidence is related to localisation of the parent company.

Type 4: Firms which are sold

In the latter type of trajectory, firms are bought by industrial groups after proving themselves. Included in this category are firms such as Appligene (founded in 1985, with an 80% takeover by the US company Oncor in 1995, and Appligene Oncor then bought out in 1999 by the Canadian Quantum), Systemix (founded in 1988, bought out by Sandoz in 1992) and Agrogene (founded in 1989 and progressively bought out by Limagrain before take over by Perking Elmer), which differ from subsidiaries created *ex nihilo* (Type 3) in so far as they are initially independent. Take-overs can be explained by problems encountered by some SMEs (difficulty in gaining access to the market, incomplete technological base) and by the purchaser's intentions. The take-over must be considered as a step in the development of the SME and not as a sign of failure. The purchaser's intention is either to complete its technological base by adding the SME's portfolio of patents or technological competency, or to use the SME to facilitate its commercial growth. In the latter case, seldom mentioned, the purchaser is often a foreign group. The SME then acts as a bridgehead in France to transfer technologies or products developed by the parent company.

A take-over generally leads to significant changes in biotech SMEs, for these firms were initially created to support an independent activity that ends up having to serve the interests of its main shareholder. If the SME was bought to be a bridgehead in Europe or France (e.g. Oncor's take-over of Appligene or Perkin Elmer's buy-out of Agrogene), its research activities will probably be scaled down to ensure there is no duplication with the parent company's R&D effort. In some cases problems arise due to a culture shock between different companies or sectors, necessitating a sufficiently long period of transition before the benefits of such restructuring can be reaped.

We cannot talk here of proximity, whether geographic or organisational, for the aim is of a totally different nature. On the other hand, the localisation of the firm plays an important role since it is often a Trojan horse enabling a bigger firm to penetrate a geographic market to which it does not have access otherwise.

Conclusion

Based on a statistical analysis of the regional location and growth of biotech SMEs in France, this article considers the dynamics of localisation of firms when they set up, and the influence of geographic environment on their development. At the time of creation, geographic proximity with the initial networks of the entrepreneur (often from the public or private research community) impacts strongly on the firm's localisation. Geographic proximity enables the firm to establish itself soundly in its local environment, and organisational and geographic proximity merge. It is one of the reasons why the impact of regional public policy in favour of firm's creation is so strong. As the firm grows, organisational proximity dominates and the firm moves away from geographic proximity since its market and field of reference are often international.

As in traditional sectors, certain elements influence biotech firms' choice of locality. Local infrastructure (incubators, support activities, innovation missions, etc.) play a key part in firms' localisation. For some firms with technological needs that they cannot meet on their own, the existence of a technological platform is essential. For these firms, whose development is science-based, proximity with high-quality academic research is important. Such research provides a favourable cultural and scientific environment to attract able researchers likely to cooperate with the firm and thus enhance its scientific potential and reputation.

Even if, in high-tech sectors with an international profile, the importance of geographic proximity decreases as the firm grows, localisation in a dynamic scientific environment suited to the emergence of new activities is essential at the time of creation. Regional policies thus have a strong impact on a firm's initial location, simultaneously creating self-reinforcing effects on a given geographic area and agglomerations of firms.

While policies in favour of business creation seem to combine harmoniously on the different levels of public intervention (municipal, regional and national), the problem of firms' survival after two or three years is a very real one in an industry characterised by rapid technological change. Further studies have to examine the development of firms in each region to evaluate the impact of each factor (public policy in favour of start-ups and geographic spillovers). Other works would also examine the linkages between the scientific notoriety and the development of firms in a region.

In France there is diversity in the modes of development of biotech SMEs, adapted to the projects of their directors and shareholders. The path of "success", where the firm tries to grow as fast as possible and aims at becoming world leader in its sector and in the stock market, is not the only possible one for biotech firms. It is probable, however, that from their creation firms in the biotech sector condition their future and growth trajectory, depending on the amount of initial investments, the networks to which they have access, the partnerships they form and whether or not they choose to appeal to outside investors. Policies supporting innovation and high-tech SMEs have to take this into account, or they may well set viable firms on paths that prove to be nothing more than a lure.

Box 1: Data collected by means of the questionnaire

- Identity of the firm and the top managers, with position
- Main technologies developed and implemented by the firm (to be ticked off on a list of 33 technologies)
- Main areas of activity (markets) in which the firm is active (to be ticked off on a list of 28 markets)
- Turnover, R&D spending, net and effective income for past three years
- Patents owned and exploited by the firm
- Quality control in the firm
- Effective and hoped for partnerships for research, production and commercialisation.

On the initiative of the MENRT Technology Division (Biotechnology group)[6] a survey was made of firms performing biotechnology research. Biotechnology firms were considered to be those that develop or use industrial technologies derived from life science and technology (and sometimes materials) using the properties of living organisms for producing goods and services (definition proposed by the Industry Ministry, "*Les 100 technologies clés à l'horizon 2000*").

The survey consisted of several stages:

1. Compilation of list of organisations (firms, economic interest groups, and associations) engaged in biotechnology research, from available sources.
2. Validation of list and addition of information, by local experts.
3. Definition of list of 478 target organisations, irrespective of size or status (SA, non for profit organisations).
4. Administration of the questionnaire.
5. Processing of data and compilation of a directory.

221 answers were registered but remained largely incomplete. In order to obtain a representative sample, the data base thus obtained was enhanced with various other available data bases: a base constituted by the INRA/SERD (Economy and Management of Research and Development) team (Lemarié and Mangematin, 2000), the France Biotech base, the Genetic Engineering Directory, Infogreffe and Diane. Missing information was thus obtained and certain firms were added to the base when all the required information was available.

In order to standardise the answers, only registered companies (SA, SARL, SNC (Société en Nom Collectif)) were selected. To ensure the relevance of comparisons with information published by Ernst & Young (1999), we analysed only those firms with under 500 employees. Finally, we excluded the rare biotech firms created before 1960. The base used in our analysis consisted of 194 firms, for which full information was available. Several indications allow us to consider the analysed sample as representative: over 60% of the firms in the France Biotech directory and 90% of the firms present in the Genetic Engineering Directory answered the questionnaire. When we analysed the base of 600 firms to which the questionnaire was sent, fewer than 450 corresponded to the selected criteria. We can therefore see that the sample analysed corresponds to roughly half of the biotech firms active in France.

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Notes

[1] Because of their recent creation, biotechnology firms are often SMEs. The average size of these firms is 40 people.
[2] This figure does not take into account divisions in certain firms with over 500 employees, specialised in biotechnology.
[3] Sessi, 1999: "La Situation de l'Industrie", Annual Business Survey, Sessi, Paris.
[4] SARLs are companies with F50,000 start-up capital and a minimum of three shareholders. The sale of shares has to be approved by all the partners. A SARL cannot be listed on the stock exchange. SAs are firms with start-up capital of at least F250,000 and a minimum of five shareholders. When they expand, SAs can be listed, under certain conditions.
[5] When comparing France, U.K. and Germany biotech specialisation, Lemarié, de Looze and Mangematin (1999) confirm that specialisation can be defined by the couple targeted market and technologies.
[6] A steering committee consisting of Pascale Auroy (ARD), Christine Bagnaro (ANVAR), Patrice Blanchet (DTA/2, MENRT), Marie José Dudézert (DTA/2, MENRT), Anne Sophie Godon (Arthur Andersen) and Vincent Mangematin (INRA/SERD) met under the chairmanship of Jean Alexis Grimaud in 1998–99 to plan and conduct the survey.

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